Survival and engraftment of dopaminergic neurons manufactured by a Good Manufacturing Practice-compatible process.

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Public Summary:
BACKGROUND AIMS: We have previously reported a Good Manufacturing Practice (GMP)-compatible process for generating authentic dopaminergic neurons in defined media from human pluripotent stem cells and determined the time point at which dopaminergic precursors/neurons (day 14 after neuronal stem cell [NSC] stage) can be frozen, shipped and thawed without compromising their viability and ability to mature in vitro. One important issue we wished to address is whether dopaminergic precursors/neurons manufactured by our GMP-compatible process can be cryopreserved and engrafted in animal Parkinson disease (PD) models. METHODS: In this study, we evaluated the efficacy of freshly prepared and cryopreserved dopaminergic neurons in the 6-hydroxydopamine-lesioned rat PD model. RESULTS: We showed functional recovery up to 6 months post-transplantation in rats transplanted with our cells, whether freshly prepared or cryopreserved. In contrast, no motor improvement was observed in two control groups receiving either medium or cells at a slightly earlier stage (day 10 after NSC stage). Histologic analysis at the end point of the study (6 months post-transplantation) showed robust long-term survival of donor-derived tyrosine hydroxylase (TH)(+) dopaminergic neurons in rats transplanted with day 14 dopaminergic neurons. Moreover, TH(+) fibers emanated from the graft core into the surrounding host striatum. Consistent with the behavioral analysis, no or few TH(+) neurons were detected in animals receiving day 10 cells, although human cells were present in the graft. Importantly, no tumors were detected in any grafted rats, but long-term tumorigenic studies will need to determine the safety of our products. CONCLUSIONS: Dopaminergic neurons manufactured by a GMP-compatible process from human ESC survived and engrafted efficiently in the 6-OHDA PD rat model.

Scientific Abstract:
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